The Significance of "Albuminuria" (Proteinuria)

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SUMMARY

"Albuminuria" is an inadequate term; proteins other than albumin commonly appear in the urine.

Proteinuria seems to depend upon failure of the tubules to reabsorb protein which has filtered through glomeruli. Its occurrence may be the result of abnormal plasma proteins, glomeruli or tubules. Proteinuria need not always be the result of a renal lesion, but may actually cause one.

When proteinuria is discovered, it should arouse curiosity about the patient in general, not merely about his kidneys. Other clinical information is needed in order that treatment be directed appropriately.

THE heat and acetic acid test for "albumin" in the urine has now been in use for two and one-half centuries; particularly since the reports of Richard Bright over 100 years ago, a positive reaction to the test has generally been considered indicative of kidney disease and is too often regarded as evidence of nephritis. Actually, "albuminuria" is found in a great variety of conditions, both with and without anatomic renal abnormalities.

We are just coming to realize the qualitative as well as quantitative limitations of this remarkably ancient method of urinalysis. In the first place, albumin is not the only protein which will precipitate from acid urine under the influence of heat; so will the several globulins normally present in the plasma, as well as hemoglobin and Bence-Jones protein which are occasional abnormalities. Even when albumin is truly present, and especially when it is in large quantities, the normal globulins also escape into the urine.[20] Perhaps the urinary loss of complement and of gamma globulin with its antibodies may be related to the well-known susceptibility to infection of individuals with the nephrotic syndrome.

The fundamental mechanisms responsible for proteinuria are not yet fully understood. It was made clear by Bieter[6] some years ago that certain methods which produced proteinuria in fish possessing glomeruli failed completely to do so in species in which the kidneys were aglomerular; protein must pass via the glomerular filtrate before it appears in the urine. On the other hand, glomerular filtrate has been regarded as protein-free in the absence of glomerular injury. Normal urine is also apparently free from protein until more sensitive tests are employed, whereupon it is found that even normal individuals excrete protein (at a rate of less than 0.1 gm. daily). There is probably no fluid in the body which is entirely free from protein, and more recent studies [8, 22, 28, 32, 33] have in fact succeeded in demonstrating the presence of protein in mammalian glomerular filtrate. Assuming[13] even as little as 10 mgm. of protein per 100 cc., the daily production of 180 liters of glomerular filtrate should contain 18 gm. of protein. More than 17.9 gm. has disappeared before the urine is completely elaborated, and this has almost surely been reabsorbed by the renal tubule cells.

Proteinuria, then, could occur with normal glomeruli whenever the tubules are unable completely to reabsorb the proteins of the glomerular filtrate. The tubular load would be greater if more protein filtered past the glomeruli; this occurs with normal plasma proteins and diseased glomeruli, but could also result even with normal glomeruli if the plasma contained proteins with physicochemical properties (size and shape in particular) which facilitated their passage through normal capillaries of the tufts; hemoglobin, egg-albumin and the Bence-Jones protein seem to be such proteins.[4, 8] Finally, it appears that the tubules cells may become functionally and anatomically damaged under conditions of this sort,[2, 12, 25] eventually allowing passage of yet more protein with final disorganization of the kidneys.

The proteins in question need not be exotically abnormal ones. Thorn induced proteinuria, in patients with chronic hepatitis but previously without proteinuria, by repeated infusions of human serum albumin.[31] Others have since provoked proteinuria in entirely normal human subjects by similar means, extending earlier observations of the same sort in experimental animals.[24] Such proteinuria in the absence of a primary renal lesion might conceivably occur as the result of spontaneous aberrations in the formation of the plasma proteins; from time to time it has been suggested that pure lipoid nephrosis is a metabolic disturbance rather than primarily a renal one.[17] Addis has shown decisively in at least one patient[2] that it is possible to observe proteinuria before the appearance in the urine of casts and especially renal tubular cells—that is, before objective evidence of a renal lesion. Others have recorded hypoproteinemia and edema preceding proteinuria in rare instances,[15, 18] and there is even a poorly documented report of normal renal tissue by biopsy early in the course of the nephrotic

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syndrome. The relative importance and frequency of this sequence of events remain to be determined, but it should be noted that Addis[3] has seen a score of patients in whom he considered that tubular degeneration was caused by abnormalities of plasma protein formation.

Quantitatively, the heat and acetic acid test leaves much to be desired. Measurements of the rate of proteinuria in grams per 24 hours are a diagnostic aid as well as a necessity before dietetic therapy. The normal minute rate of proteinuria occasionally yields a cloud when heated acid urine is sufficiently concentrated, while minor degrees of abnormal proteinuria are lost in dilute specimens. Moreover, differential diagnosis is facilitated: 20 gm. of protein per day, for example, is found in glomerular nephritis but not with pyelonephritis, renal arteriosclerosis, orthostatic albuminuria, etc.[3]

One may observe variable rates of proteinuria under certain conditions, as with the upright position or exercise in subjects with orthostatic albuminuria. In this state, careful search usually reveals casts and renal cells indicative of a transitory renal lesion which disappears *entirely* soon after the recumbent position is reached;[27] it is occasionally necessary to have the subject empty the bladder after he has been in bed for an hour or two (voiding without arising) before starting the collection of nocturnal urine. In view of the preceding discussion, it might be recorded here that in some subjects with orthostatic albuminuria the diurnal appearance of proteinuria fails to precede that of casts and renal cells in the urinary sediment; all occur simultaneously within an hour or so after the subject stands. Attention might also be directed again to the occasional gross abnormalities found by intravenous pyelography of such subjects.[26] In a unique patient, proteinuria (noctalbuminuria) appeared only during the hours of sleep,[14] a finding which reminds one of individuals with paroxysmal nocturnal hemoglobinuria.

Even when there is an underlying renal disorder which is presumably constant, the rate of proteinuria is variable. It is increased by the upright position, exercise and fever.[5] Similar increases follow the infusions of albumin into patients with the nephrotic syndrome,[21, 30] as they do after transfusions of plasma or whole blood. Congestive heart failure elevates the rate, or at times appears to provoke proteinuria. Conversely, rest in bed diminishes the rate of proteinuria, but this is not to be taken as a therapeutic suggestion for the patient with a chronic renal lesion. Some observers have found that the administration of alkalies reduces proteinuria,[5] abolishes it in some subjects with benign proteinuria, and even prevents it after exercise. This phenomenon may be related to, but is as yet distinct from, the solidification of protein into casts;[22] in this connection, the earlier alleged value of alkalinizing the urine after intravascular hemolysis has been questioned.

Increased rates of proteinuria have also been found during periods of high protein intake by patients with chronic glomerular nephritis;[5, 7, 16] such diets have similar effects in animals with experimental renal disorders.[1, 11] It is also true that low protein diets are followed by less proteinuria, but this is not thought to be the reason for the efficacy of such diets in therapy; the work of Addis[3] should be consulted on this point.

Variations in the rate of proteinuria are not necessarily accompanied by parallel changes in the intensity of the renal lesion or by fluctuations of renal function in the clinical sense. We have failed to find increases in rates of excretion of casts or of renal tubular epithelial cells when infusions of human albumin magnified proteinuria in patients with the nephrotic syndrome, and have observed simultaneous reductions in previously elevated concentrations of creatinine and urea in the serum of those individuals. It seems likely that at least the more abrupt alterations in rate of proteinuria are brought about by variations in renal blood flow and glomerular filtration rate, as well as by changes in the concentration of albumin in the serum.

It scarcely need be said that one does not treat the symptom "albuminuria," but rather the patient whose urine contains protein. Even a diagnosis is not sufficient; therapy also depends upon the patient's story, complaints, and the results of physical examination and of a few, simple laboratory procedures. Among the latter are a reliable measure of one of the non-protein-nitrogenous substances in the serum for the detection of renal insufficiency, and roentgenograms of the kidneys (preferably with intravenous pyelography) when chronic pyelonephritis is suspected. Even more important is the intelligent examination of satisfactory specimens of urine, with particular reference to the sediment and sometimes to bacteriologic study.

In some patients it will be found that no treatment at all is indicated, as when proteinuria appears only after exercise, cold showers, or injections of epinephrine, or when it occurs in individuals with sunburn or orthostatic albuminuria.

At other times the kidneys may be ignored at least temporarily while therapy is directed elsewhere. For example, penicillin is needed for the nephrotic syndrome in early syphilis, or British anti-Lewisite (BAL) for mercury poisoning, or surgical relief of the obstructive jaundice which has produced "bile nephrosis," etc. The need for extrarenal measures is even more important in the toxemia of pregnancy, and it should be remembered that minor degrees of proteinuria and elevation of non-protein-nitrogen in the serum do not contraindicate the use of diuretics when congestive heart failure is the chief problem.

At still other times, treatment of the patient with proteinuria and a chronic renal lesion (glomerular nephritis, pyelonephritis, polycystic kidneys, etc.) consists primarily of an adjustment in his protein intake. In this discussion of the significance of proteinuria there is no place for any extensive

section on dietetic management, but one point is both pertinent and important: It is imperative that the rate of proteinuria be measured occasionally so that amounts of protein equivalent to the daily loss can be added to the restricted intake in order to assure adequate nutrition.[3]

Other problems in treatment can be no more than mentioned: small amounts of sulfonamides in chronic pyelonephritis, adjustments in the intake of sodium salts during the nephrotic syndrome or with uremia, the use of Southey's tubes or infusions of albumin for edema.

ADDENDUM

Five important contributions relating to the mechanism of proteinuria have become available since this review was submitted for publication. Bull[10] has found increased pressure in the tributaries of the inferior vena cava in subjects with orthostatic proteinuria; he offers evidence that this syndrome results from compression of the vena cava by the liver. Whipple's group[29] studied the effects of raising the serum protein concentration in dogs by means of infusions of plasma; massive proteinuria so produced cleared within one to four days after the last infusion, and the kidneys were normal histologically. Lippman[19] reported that the clearance of hemoglobin by the rat kidney was doubled by intraperitoneal injections of bovine albumin; he suggested that the tubular protein reabsorption mechanism was saturated and that glomerular permeability to hemoglobin increased under the experimental conditions. Brandt and Gruhn[9] provoked proteinuria in rabbits by strongly pressor doses of renin. Their data permitted calculation of the concentration of protein in glomerular filtrate, which was found to be of the order of 11 to 33 mgm. per 100 cc., and they concluded that renin did not increase glomerular permeability to hemoglobin. Oliver[23] has described in detail the structural changes which appear in the cells of the proximal convoluted tubules during experimental proteinuria.

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